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EXAMINER
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,665	NIELSEN ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-58,69,70 and 74-77* is/are pending in the application.

4a) Of the above claim(s) *69 and 70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-58,74-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 January 2010 has been entered.

Status of Claims

2. The amendment filed on 11 January 2010 has been entered into the record and have been fully considered. Claims 54, 57 and 58 are amended. Claims 1-53, 59-68 and 71-73 are cancelled. New claims 74-77 have been added. Claims 69 and 70 have been withdrawn by Applicant as directed to non-elected invention. Claims 54-58, 69-70 and 74-77 are pending in the instant application.

Traversal of withdrawal of claims 69 and 70

3. Applicants traverse the withdrawal of claims 69 and 70 from examination. Applicants argue that claim 69 reciting administering an EPO mutein prior to a surgical procedure falls within the scope of claim 57 that recites “a method for

protecting against or preventing a tissue injury" and the species election of "retinal ischemia". Applicants therefore, request the withdrawal of species election.

4. Applicant's arguments are fully considered but not found to be persuasive, because as per restriction requirement dated 6/20/06 pages 17-19, Applicant elected "retinal ischemia" as the species of injury (see Applicant's response dated 12/20/06, page 5, election (h)). Since each of the listed injury type will involve different cell types, determine characteristically different pathology, requiring different treatment strategies, from one another, each will represent a patentably distinct invention and would require a separate search of the art that would be burdensome to the examiner. Besides the limitations 'surgical procedure', or a 'cardiopulmonary bypass surgery', of claims 69 and 70 form a different species commensurate with the original "heart-lung bypass" (see Office Action dated 6/20/06, page 18, species number (xxvii)) species, that is distinct from the elected "retinal ischemia" (species (xxxiii)). Claims 69 and 70 are therefore, withdrawn as directed to non-elected species.

5. The requirement is still deemed proper and is therefore made FINAL.

6. Claims 69 and 70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Although all elections were made with traverse in the reply filed on 20 December 2006, Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement or in the

species election requirement, therefore all elections have been treated as an election without traverse (MPEP § 818.03(a)).

7. Claims 54-58, and 74-77, drawn to a method for protecting, maintaining or enhancing the viability of a responsive cell or tissue in vivo or ex vivo, are under consideration in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

8. Upon re-consideration of current claim amendments, the rejection of claims under obviousness double patenting over US patent 6531121, application numbers 10/188905, 10/351640 (now abandoned), 10/185841 (now US Patent number 7767643), 09/716960 (now US Patent number 7410941), and 10/573905 (US Patent number 7645733), have been withdrawn.

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 54-58 and 74-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 74-75 are rejected, as being vague and indefinite, because the definition of “non-conservative substitution” in the instant specification contradicts with the mutations listed in the claims. Based upon the instant specification, a conservative substitution “takes place within a family of amino acids”, such as acidic, basic, non-polar, polar, aliphatic, etc. (paragraph spanning pages 46 and 47). The specification also provides the different amino acids that can be grouped in these families. For example, valine and serine can be grouped as aliphatic, therefore, would comprise a conservative substitution (i.e. aliphatic to aliphatic substitution) as in V11S. Therefore, V11S (see claims 74, 75) cannot be a non-conservative substitution. Similarly, T44I, S100A, etc. are not non-conservative per definition in the instant specification. Appropriate clarification and correction is required.

11. Claims 54-58 are rejected because dependent claims 74 and 75 limit the non-conservative substitution as comprising both conservative and non-conservative amino acid changes (see preceding paragraph). The claims fail to identify the metes and bounds of the related subject matter and how that could be ascertained in the stated invention.

35 U.S.C. § 112, first paragraph – Scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 54-58 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of protecting, maintaining or enhancing the viability of an erythropoietin-responsive cell, tissue or organ isolated from a mammalian body; or a method of protecting tissue injury, or restoring or rejuvenating tissue function in a mammal wherein the tissue is responsive to EPO; comprising exposing said cell, tissue or organ, in vivo or in vitro to a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine comprising SEQ ID NO: 10 with a non-conservative substitution of an amino acid residue, wherein the said mutein consists of S100E, R150E, R103E K45D or K45D/S100E, or has a substitution of amino acid arginine in position 103, and has a reduced level of in vivo erythropoietic activity; does not reasonably provide enablement for the method comprising exposing said cell, tissue or organ in vivo or in vitro, to a pharmaceutical composition comprising any mutein recombinant tissue protective cytokine comprising SEQ ID NO: 10, with a substitution of any amino acid residue at one or more positions of SEQ ID NOs: 1, 2, 3 or 4, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the inventions commensurate in scope with these claims.

13. The claims recite ex vivo method of protecting, maintaining or enhancing the viability of a responsive cell (neuronal or ganglion), or an organ comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a mutein tissue protective cytokine comprising the amino acid sequence of SEQ ID NO: 10, with a non-conservative substitution of an amino acid residue at one or more position of SEQ ID NOs: 1, 2, 3 or 4; has reduced in vivo erythropoietic activity; and has tissue protective activity (claims 54-56). Claims 57-58 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, or restoration or rejuvenation of tissue or tissue function, in a mammal using the above muteins, wherein the mammal has or is at risk of diseases and injuries, e.g. retinal ischemia. Claims 74-75 recite non-conservative substitutions.

14. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

15. The nature of the instant invention is the demonstration that the administration of or exposure of cells to erythropoietin (EPO) - or a particular

recombinant erythropoietin such as the muteins K45D, R103E, R150E, S100E, and S100E/K45D - is capable of protecting cells and tissues from tissue injury, such as retinal ischemia. The specification teaches that conservative or non-conservative amino acid substitutions can be made at one or more residues of EPO (paragraph spanning pages 46 and 47). The instant specification demonstrates that recombinant EPO muteins K45D and S100E provide neuroprotection to SK-N-SH neuroblastoma cells in culture (Example 3); EPO can cross the blood-brain barrier (Example 2) and the blood-eye barrier (Example 9); treatment with S100E enhance the viability of PC12 cells subjected to NGF withdrawal in culture (Example 16); the muteins S100E, R103E and R150E each have several orders of magnitude lower potency than EPO in an UT-7 cell bioassay, whereas the K45D variant demonstrated a potency equivalent to EPO (UT-7 is a leukemia EPO-dependent cell line used for the determination of the erythroid effect of recombinant tissue protective cytokines) (Example 17); and finally, treatment with R103E, R150E, S100E or S100E/K45D in a rat reversible glaucoma model subjected to retinal ischemia resulted in reducing injury (measured by comparative electroretinograms of peak amplitude latency in the injured and uninjured eyes), when compared to saline treated rats and was equal or better than EPO- treated rats (Example 18).

16. The state of the art recognizes the neuroprotective effects of EPO in animals administered with EPO (Brines et al. (2000) Proc Natl Acad Sci USA, 97(19): 10526- 10531 - listed on Applicant's IDS). The art also recognizes that

the in vitro and in vivo ischemic injury models employed in the instant disclosure are associated either directly or indirectly with inflammation, immune-mediated inflammatory responses, or apoptosis (Brines et al. pg 10531; Rosenbaum et al. Vision Res. 37(24): 3445-3451, 1997). Applicant's invention is predicated on similar findings, i.e. EPO has a neuroprotective effect as well as being able to reduce retinal ischemic damage. The art recognizes that various cells and tissues express erythropoietin receptors, such as neurons, hematopoietic cells, kidneys, heart tissue, and adrenal cortex and medulla (Juul et al. (1998) Pediatr. Res, 43: 40-49, and Westenfelder et al. (1999) Kidney Intl. 55: 808-820; both listed on Applicant's IDS).

17. Claims 54-58 broadly read on a large number of sequences with one or more non-conservative amino acid substitutions in SEQ ID NOs 1-4. However, the listing of preferred non-conservative substitutions in claims 74 and 75 appears to contradict the teaching in the instant specification. As stated above, a conservative substitution “takes place within a family of amino acids”, such as acidic, basic, non-polar, polar, aliphatic, etc. (paragraph spanning pages 46 and 47). However, claims 74 and 75 lists substitutions that are conservative as per the teaching in the instant specification. Please note that with regard to the claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of

the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification.

As such the broadest reasonable interpretation of the amended claims would be an ex vivo or in vivo method encompassing the use of a mutein tissue protective cytokine comprising the peptide sequence of SEQ ID NO: 10, with a **non-conservative or conservative** substitution of one or more amino acid **with any amino acid** in SEQ ID NOs: 1, 2, 3 or 4, wherein the mutein has a reduced in vivo erythropoietic activity and, wherein the mutein has tissue protective activity (emphasis added).

18. The specification teaches the making of muteins by various modifications including substitution, addition, and deletion of amino acids in SEQ ID NOs: 1-4 and various other positions (pages 4-9; 32-35; 47-49), that can be tested and used for tissue protection. However, the specification has not provided sufficient guidance about specific muteins with substitution at specific amino acid residues and demonstrating the claimed properties. This information is essential to the skilled artisan because in all likelihood all sequences identical to SEQ ID NO: 10 and having one or more substitution in the above 4 regions will not result in the desired activity. For example, Gantier et al. (US PGPB 20080194477A1, dated 8/14/2008) teach a modified EPO peptide (para 0357) of sequence (SEQ ID NO: 942), that is identical to the instant SEQ ID NO: 10, except for a point mutation in amino acid position 45 (K45Q) (see attached Appendix A for SCORE sequence alignment submitted 12/11/2008). The reference teaches that the modified

cytokine and EPO peptides have increased bioavailability and increased resistance to proteolysis (para 0258-0259), however, have the same therapeutic properties of the unmodified cytokine involving erythropoietic activity, such as in red blood cell expansion, anemia, renal failure, cancer etc. (para 0443; Table, page 103). The reference also provides various modifications by substitution of amino acids in the EPO sequence, many of which are within the regions of the instantly claimed SEQ ID NOs: 1-4, wherein all muteins protect against proteolysis without the reduction in erythropoietic activity (Figure 12L). Sytkowski et al. (US Patent number 6489293, 3 December 2002) teach that substitution of alanine in 100 position for serine (S100A), or for glycine in position 101 (G101A), results in increased specific erythropoietic activity, such as the ability to regulate growth and differentiation of red blood cell progenitor cells with respect to EPO (Table 1; col 9, para 2). Please note that S100A, recited in claims 74 and 75, is a conservative substitution of amino acids serine to alanine (i.e. aliphatic to aliphatic). Sytkowski et al., however, teach the importance of position 103 in the EPO amino acid sequence, demonstrating that replacing arginine 103 with another amino acid, results in significant drop in erythropoietic specific activity (col 3, para 5; Tables I, II). The above citations go on to prove that any substitution of amino acids in the recited sequences will not result in non-erythropoietic muteins. With the exception of muteins S100E, R103E, R150E, K45D, K45D/S100E, the instant specification has not provided guidance on the broad genus of muteins as claimed. Without this information the specification's

general discussion of making and using of muteins constitute an invitation to experiment by trial and error. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Based on the broad genus of muteins as recited in the amended claims, a skilled artisan will require undue experimentation to test the enormous number of putative muteins, involving the substitution of any one of 19 other amino acid residues in 28 different positions (derived from SEQ ID NOs: 1-4) of SEQ ID NO: 10, which corresponds to 28^{19} potential muteins. Undue experimentation would be required by the skilled artisan to determine such.

19. That single amino acid changes in the amino acid sequence of a protein can have dramatic effects on the protein's function or structure is further exemplified in the teachings of Boissel et al. (WO 94/24160, published October 27, 1994). The reference demonstrates that replacement of particular residues, such as Lys140, Arg143, Ser146, Asn147 or Lys154, with alanine resulted in an EPO molecule with significantly increased (3-fold) biological activity, whereas replacement of a tyrosine residue (Tyr156) with alanine resulted in a molecule with slightly decreased biological activity (pg 69, lines 2-11; Figures 19-22). The

art thus recognizes unpredictability in the biological activity of modified EPO molecules according to recited modifications encompassed by the instant invention in that certain modifications, such as substitution of particular amino acid residues, result in EPO molecules with enhanced biologically activity rather than the desired decreased or deficient biological activity (a good example being S100A as explained above). It would thus appear that certain mutein recombinant cytokine molecules would be potentially inoperative as they are currently broadly recited, requiring undue experimentation of the skilled artisan to determine which particular recombinant molecules retain the desired tissue protective ability and are thus suitable for practicing the claimed methods.

20. Specifically, proper analysis of the Wands factors was provided in the previous Office Action. Therefore, in view of the breadth of the claims still encompassing an enormous number of muteins, the lack of adequate guidance or evidence supporting a therapeutic effect of the same, the unpredictability in the art of biological effects of modifying EPO molecules by substitution of any amino acid, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

Applicant's remarks

21. Applicant argues that the current claim amendments to recite non-conservative substitution of amino acids in SEQ ID NOs: 1-4 reduces the number of possible muteins encompassed by the claims. Applicant asserts that because the regions specified in the amended claims are required for erythropoietic activity of EPO, a non-conservative amino acid substitution "is likely to reduce the erythropoietic activity of EPO". Applicant further adds that the working examples demonstrate that the muteins with non-conservative substitutions - S100E (uncharged polar to acidic), R150E, R103E, K45D (all basic to acidic) and K45D/S100E, despite having reduced erythropoietic function, elicit tissue protective activity. Applicant argues that identifying and testing such EPO muteins for the claimed tissue protective function would not entail undue experimentation. Applicant further argues that Gantier, a post-filing reference, only provides a "generic roadmap for making cytokine mutants (including EPOs) that protect against proteolysis and which retain their biological function". Applicant alleges that Gantier does not provide any evidence that the biological activity retained by some or all of the EPO muteins is erythropoietic activity. For example, the Table at page 103 lists biological functions maintained by the muteins that are not limited to erythropoietic activity. Applicant therefore, concludes that Gantier cannot serve as an evidence for non-enablement for the instant claims. Applicant believes that there will not be any more than routine

experimentation in making and practicing the invention as set forth in the amended claims, therefore, requests the withdrawal of the rejection.

22. Applicant's arguments are fully considered, however, are not found to be persuasive. Firstly, Examiner acknowledges the removal of the terms "prevention" and restoring or rejuvenating "tissue" from claim 57. Examiner also agrees to Applicant's comments asserting the evidence of specific muteins in working examples demonstrating the claimed activity in vitro or in vivo or both. Examiner understands that muteins S100E, R103E, R150E, K45D, K45D/S100E are appropriate examples of non-conservative amino acid substitution as explained by Applicant, and these demonstrate tissue protection, especially S100E and R103E for in vivo reduction of retinal injury and spinal cord injury. However, as stated above, the claims although requiring only non-conservative substitution, include both conservative and non-conservative in the mutein listing as recited in dependent claims 74 and 75. Because a dependent claim should be further limiting the breadth of the claim/s from which it depends, independent claims 54 and 57 would also be interpreted to include conservative and non-conservative amino acid substitutions. Applicant's reference to teachings of non-conservative substitution muteins in the instant specification is not found to be persuasive, as these citations are not exclusive for non-conservative substitution. The same argument holds true for Applicant's remarks dated 6/30/08 attached as Exhibit A.

23. Applicant's remarks with respect to Gantier's teachings are not found to be persuasive. While Applicant is right that there may be other activities in addition to erythropoietic activity of EPO that are maintained by the mutants, Gantier clearly demonstrates that the said mutations do not elicit a reduced hematopoietic activity of EPO as required by the instantly claimed mutants. While true that the person of ordinary skill will be able to make mutants by standard protocols, the skilled artisan will be subjected to undue experimentation in identifying and testing the muteins for reduced erythropoietic activity and tissue protective activity.

This rejection could be overcome by inserting the limitations of claims 76 and 77 in the independent claims 54 and 57 respectively.

112-1st paragraph – Written Description

24. Claims 54-58 and 74-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

25. The claims recite ex vivo method of protecting, maintaining or enhancing the viability of a responsive cell (neuronal or ganglion), or an organ comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a mutein tissue protective cytokine comprising the amino acid sequence of SEQ ID

NO: 10, with a non-conservative substitution of an amino acid residue at one or more position of SEQ ID NOs: 1, 2, 3 or 4; has reduced in vivo erythropoietic activity; and has tissue protective activity (claims 54-56). Claims 57-58 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, or restoration or rejuvenation of tissue or tissue function, in a mammal using the above muteins, wherein the mammal has or is at risk of diseases and injuries, e.g. retinal ischemia. Claims 74-75 lists the non-conservative substitutions of amino acids.

26. The instant specification demonstrates that the administration of or exposure of cells to EPO muteins - K45D, R103E, R150E, S100E, and S100e/K45D - is capable of protecting cells and tissues from tissue injury, such as retinal ischemia. The specification also teaches that conservative or non-conservative amino acid substitutions can be made at one or more residues of EPO (paragraph spanning pages 46 and 47). The instant specification demonstrates that recombinant EPO muteins K45D and S100E provide neuroprotection to SK-N-SH neuroblastoma cells in culture (Example 3); EPO can cross the blood-brain barrier (Example 2) and the blood-eye barrier (Example 9); treatment with S100E enhance the viability of PC12 cells subjected to NGF withdrawal in culture (Example 16); the variants S100E, R103E and R150E each have several orders of magnitude lower potency than EPO in an UT-7 cell bioassay, whereas the K45D variant demonstrated a potency equivalent to EPO (UT-7 is a leukemia EPO-dependent cell line used for the

determination of the erythroid effect of recombinant tissue protective cytokines) (Example 17); and finally, treatment with R103E, R150E, S100E or S100E/K45D in a rat reversible glaucoma model subjected to retinal ischemia resulted in reducing injury (measured by comparative electroretinograms of peak amplitude latency in the injured and uninjured eyes), when compared to saline treated rats and was equal or better than EPO- treated rats (Example 18). However, the use of non-conservative amino acid substitutions K45D, R103E, R150E, S100E, and S100e/K45D in the amino acid sequence of SEQ ID NO: 10, do not provide a description of a representative number of species and hence is not adequate written description of an entire genus of EPO muteins which would be effective to provide adequate written description of methods using an entire genus of EPO muteins capable of tissue protective activity along with reduced in vivo erythropoietic activity as broadly claimed. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, or any combination thereof, and the method of making the claimed invention. However, in this case, the specification has not shown a relationship between the structure, function, or properties of the claimed EPO muteins comprising non-conservative

substitution of amino acids.

27. The specification further adds that methods for screening combinatorial libraries of mutants are known in the art (page 45, para 2, 3; page 46, para 1). The situation is analogous to the decision in the *University of Rochester v. G.D. Searle and Co.* (69 USPQ 2nd 1886, CAFC 2004), wherein the Federal Circuit upheld the district court's ruling that patent claims which recited administration of compounds not disclosed, but rather to be identified in a screening assay, were invalid on their face. Since the specification does not disclose to the public the structures claimed, it does not meet the written description requirement of 35 USC § 112, first paragraph.

28. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

29. The skilled artisan cannot envision the entire genus of non-conservative "and conservative" EPO muteins of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*,

25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

30. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

31. Therefore, the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

This rejection could be overcome by inserting the limitations of claims 76 and 77 in the independent claims 54 and 57 respectively.

Applicant's Remarks

32. Applicant argues that the currently amended claims have defined regions comprising non-conservative substitutions that affect the erythropoietic activity of EPO, and mutations within this region yield EPO muteins that lack erythropoietic activity. Applicant further argues that specific mutein recombinant tissue protective cytokines are described in the instant specification and working examples demonstrating the reduced erythropoietic activity and the presence of tissue protective activity is exemplified in various examples. The instant specification also discloses a structure-function correlation of the muteins, so as

to prove possession of the claimed invention at the time of filing. Thus Applicants assert that the rejection for lack of written description should be withdrawn.

33. Applicant's arguments have been fully considered but have not been found to be persuasive. The amended claims are limited to methods using mutein recombinant tissue protective cytokine molecules comprising non-conservative substitution of an amino acid in one or more positions of SEQ ID NOs: 1-4 of SEQ ID NO: 10, however, the claims still fail to recite a representative number of EPO mutein species. As stated above, the claims recite a broad genus of EPO muteins comprising conservative and non-conservative amino acid substitutions in one or more positions of SEQ ID NOs: 1-4 of SEQ ID NO: 10. Hence, the specification does not provide adequate written description of methods using an entire genus of EPO muteins capable of tissue protective activity along with reduced in vivo erythropoietic activity as broadly claimed. Accordingly, there is no means by which the artisan, given any of these cytokine molecules, would know whether it was a member of the genus that could be used in the claimed methods. The instant disclosure of the several specific mutein EPO species does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of molecules.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

34. Claims 74-75, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

35. The claims recite ex vivo or in vivo method of protecting, maintaining or enhancing the viability of a responsive cell (neuronal or ganglion), or a responsive tissue in a mammal, comprising exposing said cell, or tissue to a pharmaceutical composition comprising a mutein tissue protective cytokine comprising the amino acid sequence of SEQ ID NO: 10, with a non-conservative substitution of an amino acid residue at one or more position of SEQ ID NOs: 1, 2, 3 or 4, "wherein the non-conservative substitution comprises one or more of the following amino acid changes: ….V11S,….T44I,…..F48I, F48A,…S100A,… S104A, S104I, T106A, T107L,… L108S,…" etc.

36. The specification as originally filed does not provide adequate written description for reciting **non-conservative** substitution comprising one or more of

the following amino acid changes: ….V11S,….T44I,…..F48I, F48A,…S100A,… S104A, S104I, T106A, T107L,… L108S,…" etc. The instant specification teaches a conservative substitution "takes place within a family of amino acids", such as acidic, basic, non-polar, polar, aliphatic, etc. (paragraph spanning pages 46 and 47). A non-conservative substitution would therefore, comprise substitution of amino acids outside the family of amino acids, in other words a non-conservative substitution should constitute for example - acidic to basic, etc. Please note that claims 74 and 75 include both conservative and non-conservative amino acid substitutions. The specification does not contemplate the narrowed limitation, whereby non-conservative substitution would include conservative substitution. These are not expressly asserted, nor do they flow naturally from the specification. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

37. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

38. Claims 54-58 are rejected under 35 U.S.C. 102(e) as clearly anticipated by Brines et al. (International Publication No WO 02/053580 A2, filed on 28 December 2001, with a prior filing date for US Patent application number 09/753,132, of 29 December 2000).

39. The claims recite ex vivo method of protecting, maintaining or enhancing the viability of a responsive cell (neuronal or ganglion), or an organ comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a mutein tissue protective cytokine comprising the amino acid sequence of SEQ ID NO: 10, with a non-conservative substitution of an amino acid residue at one or more position of SEQ ID NOs: 1, 2, 3 or 4, has reduced in vivo erythropoietic activity, and has tissue protective activity (claims 54-56). Claims 57-58 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, restoration or rejuvenation of tissue or tissue function, in a mammal using the

above muteins, wherein the mammal has or is at risk of a large number of diseases and injuries, e.g. retinal ischemia.

40. Brines et al. teach methods for protecting, maintaining or enhancing the viability of an erythropoietin responsive cell, tissue or organ in vivo, in situ or ex vivo, comprising the administration of modified EPO comprising at least one modification in amino acid sequence as compared to native EPO such as an EPO mutein (page 4, para 1, 2; claims 31-33, 36-37, 39), and which is non-erythropoietic or lacking an activity of EPO such as not causing an increase in hematocrit (page 64, para 1; page 65). The reference discloses EPO useful for the said method can be non-conservatively altered in one or more amino acids within the four sequence lengths (VLQRY, TKVNFYAW, SGLRSLTTL and/or SNFLRG) represented by the instantly claimed SEQ ID NOs: 1-4 respectively (page 24). Brines et al further teach the treatment or protection by the administration of EPO to mammals having various disorders like heart failure, retinal detachment or trauma, etc. (Table, page 46-50). The reference further teaches that the activity of EPO and EPO like molecules is based on its effectiveness in stimulating red cell production in rodent models (page 29, para 1). As Brines et al teach the structural and functional limitations of the amended claims, the reference anticipates the claimed invention.

Applicant's Remarks

41. Applicant argues that the rejection is moot as the reference does not "disclose non-conservative amino acid substitutions" as recited in the currently amended claims. Applicant therefore, requests the withdrawal of the rejection.

42. Applicant's arguments are fully considered, however, are not found to be persuasive. Contrary to Applicant's allegation, Brines et al do teach non-conservative mutations or substitutions of amino acids in the peptide lengths corresponding to the instantly claimed SEQ ID NOs: 1-4. Applicant's arguments are therefore, moot.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

43. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

44. Claims 54-58 and 74-77, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (US Patent number 6489293, dated 3 December 2002), in view of Brines et al. (International Publication No WO 02/053580 A2, filed on 28 December 2001, with a prior filing date for US Patent application number 09/753,132, of 29 December 2000).

45. The claims recite ex vivo method of protecting, maintaining or enhancing the viability of a responsive cell (neuronal or ganglion), or an organ comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a mutein tissue protective cytokine comprising the amino acid sequence of SEQ ID NO: 10, with a non-conservative substitution of an amino acid residue at one or more position of SEQ ID NOs: 1, 2, 3 or 4; has reduced in vivo erythropoietic activity; and has tissue protective activity (claims 54-56). Claims 57-58 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, or restoration or rejuvenation of tissue or tissue function, in a mammal using the above muteins, wherein the mammal has or is at risk of diseases and injuries, e.g. retinal ischemia. Claims 74-75 lists the non-conservative substitutions as involving different amino acid changes. Claims 76-77 further limits the non-conservative substitutions to include amino acid changes - K45D, R103E, R150E, S100E, and S100e/K45D.

46. Sytkowski et al. (US Patent number 6489293, 3 December 2002) teach the identification of features of EPO protein relevant to its structure and function. The reference teaches modified secretable EPO proteins, wherein at least one amino acid residue in Domain 1 (amino acids 99-110) is different from that present in the same region of wild type EPO (abstract; col 3, para 2). The reference also teaches the importance of position 103 in the EPO amino acid sequence, further demonstrating that replacing arginine 103 with another amino acid, e.g. R103E, results in a significant drop in erythropoietic specific activity (col 3, para 5; Tables I, II).

47. Sytkowski et al do not teach that R103E has any other activity like protecting, maintaining or enhancing the viability of a responsive cell/tissue.

48. The teachings of Brines et al. are set forth above.

49. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the use of R103E having decreased erythropoietic activity as taught by Sytkowski et al, by using such mutein for the protection, maintenance or enhancement of viability of a responsive cell or tissue in view of the teachings of Brines et al. The person of ordinary skill in the art would have been motivated to try using R103E because it falls within the desired region of SEQ ID NO: 3 comprising amino acids 100 to 108 (as taught by Brines et al), has a non-conservative substitution, i.e. basic to acidic alteration, and because Sytkowski et al. teach that changing arginine at

103 position results in decreasing or abolishing the activity of EPO. The person of ordinary skill in the art would have expected success because efforts to obtain modified EPO molecules for various biological processes were being designed in the pharmaceutical industry at the time the invention was made.

50. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

51. No claims are allowed.

52. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

53. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

54. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
27 December 2010

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649